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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/504,280	02/15/2000	Mike A. Clark	phoe-0057	5368

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Woodcock Washburn Kurtz
Mackiewicz & Norris LLP
One Liberty Place - 46th Floor
Philadelphia, PA 19103

EXAMINER
ROMEO, DAVID S

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 04/08/2002 11

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/504,280	CLARK, MIKE A.	
	Examiner	Art Unit	
	David S Romeo	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *9-13 and 18-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 14-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Applicant's election with traverse of group II and the species succinimidyl succinate in Paper No. 7 is acknowledged. The traversal is on the ground(s) that there is not a serious burden. This is not found persuasive because an application may properly be required to be restricted to one of two or more claimed invention if they are able to support separate patents and they are either independent (MPEP § 806.04 - § 806.04 (j)) or distinct (MPEP § 806.05 - § 806.05(i)). The groups are distinct for the reasons given in the Office action mailed 06/06/2001 (Paper No. 5). Furthermore, separate classification (i.e., class and subclass) of distinct inventions is sufficient to establish a prima facie case that the search and examination of the plural inventions imposes a serious burden upon the Examiner. See M.P.E.P. § 803. Such separate classification is set forth in the Office action mailed 06/06/2001.

The requirement is still deemed proper and is therefore made FINAL. However, the examiner is open to further grouping if allowable generic subject matter can be agreed upon that encompasses the different groups.

Claims 9-13, 18-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to, or to the extent that they are drawn to, a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 7.

Claims 1-8, 14-17 are being examined to the extent that they read upon an elected invention and/or species. Citations by the examiner are in an alphanumeric format, such as

"(a1)", wherein the "a" refers to the reference cited on the Notice of References Cited, PTO-892, and the "1" refers to the Paper No. to which the Notice of References Cited, PTO-892, is attached.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following claims are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-8, 14-17 are indefinite over the recitation of "molecular weight in the range of about ..." because there or no units associated with the molecular weight range. The metes and bounds of the claim(s) are not clearly set forth.

Claim 3 recites the limitation "said linker". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 14-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Tsutsumi (AL, cited by Applicants). Tsutsumi teaches the pegylation of natural human TNF-α with N-succinimidyl succinate PEG via the formation of an amide bond between a lysine amino acid residue of TNF-α and the succinimidyl succinate group, wherein the PEG has a molecular weight of about 5,000 (page 9, column 2, full paragraph 1; page 10, column 2, full paragraph 1). The pegylated TNF-α is a modified TNF comprising TNF covalently bound to between about five and twelve PEG molecules. A molecular weight of about 5,000 is "an approximate weight average molecular weight in the range of about 10,000 to about 40,000", as recited in claim 1, "an approximate weight average molecular weight in the range of about 20,000 to about 30,000", as recited in claims 2, 15, 17, and "an approximate molecular weight in the range of 20,000 to 30,000", as recited in claim 16. The amide bond between a lysine amino acid residue of TNF-α and the succinimidyl succinate group is a covalent bond that binds the TNF to the PEG through primary amines on the TNF, as recited in claim 2. The succinimidyl succinate group is a biocompatible linker, as recited in claim 2, 15, 17. The limitations "enhancing the circulating half life" and "reducing toxicity" have not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. In any case, the pegylation enhanced the circulating half life and tumoricidal activity of the TNF in mice suffering from a tumor (Abstract; page 9, paragraph bridging columns 1-2; page 10, column 1, full paragraph 1; Figures 1 and 2), as recited in the preamble of claims 14-17. Furthermore, where the claimed and prior art products

are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, claimed properties or functions are presumed to be inherent, and a prima facie case of either anticipation or obviousness has been established. The limitation "recombinant human TNF" in claim 7 is viewed as a product-by-process limitation. Although Tsutsumi is silent with respect to "recombinant human TNF", the recitation of the product-by-process limitation is not viewed as positively limiting the TNF absent a showing that the recombinant process of making TNF recited in claim 7 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 8 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tsutsumi (AL, cited by Applicants) and Nakamura (u10). Tsutsumi teaches the pegylation of natural human TNF-α with N-succinimidyl succinate PEG via the formation of an amide bond between a lysine amino acid residue of TNF-α and the succinimidyl succinate group, wherein the PEG has a molecular weight of about 5,000 (page 9, column 2, full paragraph 1; page 10, column 2, full paragraph 1). A molecular weight of about 5,000 is "an approximate weight average molecular weight in the range of about 10,000 to about 40,000", as recited in claim 1, "an approximate weight average molecular weight in the range of about 20,000 to about 30,000", as recited in

claims 2, 15, 17, and "an approximate molecular weight in the range of 20,000 to 30,000", as recited in claim 16 The amide bond between a lysine amino acid residue of TNF-α and the succinimidyl succinate group is a covalent bond that binds the TNF to the PEG through primary amines on the TNF, as recited in claim 2. The succinimidyl succinate group is a biocompatible linker, as recited in claim 2, 15, 17. The limitations "enhancing the circulating half life" and "reducing toxicity" have not been given patentable weight because the recitation occurs in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. In any case, the pegylation enhanced the circulating half life and tumoricidal activity of the TNF in mice suffering from a tumor (Abstract; page 9, paragraph bridging columns 1-2; page 10, column 1, full paragraph 1; Figures 1 and 2), as recited in the preamble of claims 14-17. Furthermore, where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, claimed properties or functions are presumed to be inherent, and a prima facie case of either anticipation or obviousness has been established. The limitation "recombinant human TNF" in claim 7 is viewed as a product-by-process limitation. Although Tsutsumi is silent with respect to "recombinant human TNF", the recitation of the product-by-process limitation is not viewed as positively limiting the TNF absent a showing that the recombinant process of making TNF recited in claim 7 imparts a novel or unexpected property to the claimed product, as it is assumed that equivalent products are obtainable by multiple routes. Tsutsumi does not teach deleting amino acids 1-9 of the mature TNF protein.

Nakamura teaches a novel recombinant tumor necrosis factor-alpha (TNF) mutant (mutant 471), in which 7 N-terminal amino-acids were deleted and Pro8Ser9Asp10 was replaced by ArgLysArg. Mutant 471 had a 7-fold higher anti-tumor activity, and a higher binding activity to TNF receptors. The possible cachectin activity of mutant 471 was almost the same as that of wild-type TNF. The acute lethal toxicity of mutant 471 was 18 times lower than that of wild-type TNF. These results suggest that mutant 471 might be a more promising anti-cancer agent than wild-type TNF. See the Abstract. The tumor necrosis factor-alpha (TNF) mutant (mutant 471), in which 7 N-terminal amino-acids were deleted and Pro8Ser9Asp10 was replaced by ArgLysArg, encompasses a human TNF mutated by deleting amino acids 1-9 of the mature protein. Nakamura does not teach the pegylation of mutant 471.

However, it would have been obvious to one of ordinary skill in the art at the time of Applicants' invention to pegylate natural human TNF-α, as taught by Tsutsumi, and to modify that teaching by pegylating mutant 471, as taught by Nakamura, with a reasonable expectation of success. One of ordinary skill in the art would be motivated to combine these teachings because one of ordinary skill in the art would be motivated to combine the enhanced circulating half life and tumoricidal activity of the pegylated TNF taught by Tsutsumi with the higher anti-tumor activity, higher binding activity to TNF receptors, the possible cachectin activity the same as that of wild-type TNF, and the lower acute lethal toxicity of mutant 471 taught by Nakamura in order to obtain a more promising anti-cancer agent. The invention is prima facie obvious over the prior art.

Conclusion

No claims are allowable.

ANY INQUIRY CONCERNING THIS COMMUNICATION OR EARLIER COMMUNICATIONS FROM THE EXAMINER SHOULD BE DIRECTED TO DAVID S. ROMEO WHOSE TELEPHONE NUMBER IS (703) 305-4050. THE EXAMINER CAN NORMALLY BE REACHED ON MONDAY THROUGH FRIDAY FROM 7:30 A.M. TO 4:00 P.M.

IF ATTEMPTS TO REACH THE EXAMINER BY TELEPHONE ARE UNSUCCESSFUL, THE EXAMINER'S SUPERVISOR, GARY KUNZ, CAN BE REACHED ON (703) 308-4623.

IF SUBMITTING OFFICIAL CORRESPONDENCE BY FAX, APPLICANTS ARE ENCOURAGED TO SUBMIT OFFICIAL CORRESPONDENCE TO THE FOLLOWING TC 1600 BEFORE AND AFTER FINAL RIGHTFAX NUMBERS:

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FAXED DRAFT OR INFORMAL COMMUNICATIONS SHOULD BE DIRECTED TO THE EXAMINER AT (703) 308-0294.

ANY INQUIRY OF A GENERAL NATURE OR RELATING TO THE STATUS OF THIS APPLICATION OR PROCEEDING SHOULD BE DIRECTED TO THE GROUP RECEPTIONIST WHOSE TELEPHONE NUMBER IS (703) 308-0196.

David Romeo

DAVID ROMEO
PRIMARY EXAMINER
ART UNIT 1647

DSR
APRIL 7, 2002